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Moderate Exercise Improves Immunity and Decreases Illness Rates

Abstract: *Moderate exercise training causes favorable perturbations in immunity and a reduction in incidence of upper-respiratory illness (URI). During each bout of moderate exercise, an enhanced recirculation of immunoglobulins, neutrophils, and natural killer cells occurs that persists for up to 3 hours postexercise. This exercise-induced surge in immune cells from the innate immune system is transient but improves overall surveillance against pathogens. As moderate exercise continues on a near-daily basis for 12 to 15 weeks, the number of symptom days with URI is decreased 25% to 50% compared with randomized sedentary controls. Epidemiological and animal studies support this inverse relationship between URI risk and increased physical activity. Recent evidence indicates that maintaining leanness and a physically active lifestyle during adulthood reduces systemic inflammation, an underlying factor in multiple chronic diseases. The anti-inflammatory influence of near-daily physical activity in lowering C-reactive protein, total blood leukocytes, interleukin-6, and other inflammatory cytokines may play a key role in lowering risk of cardiovascular disease, certain types of cancer, type 2 diabetes, sarcopenia, and dementia.*

Keywords: upper-respiratory-tract infection; physical activity; natural killer cells; neutrophils; inflammation

Introduction

Upper-respiratory illness (URI) is the most frequently occurring infectious disease in humans worldwide.[1-3] More than 200 different viruses cause the common cold, and rhinoviruses and coronaviruses are the culprits 25% to 60% of the time. The US Centers for Disease Control and Prevention has estimated that more than 1 billion URIs occur annually in the United States, a leading cause of lost school and work days. The average person has 2 or 3 respiratory infections each year, with young children suffering 6 to 7. Non–influenza-related viral respiratory infections impart an estimated $40 billion burden in direct and indirect costs on the US economy.[2]

Lifestyle habits are strongly related to immune function. Old age, avoidance of physical activity, mental stress, poor nutrient and energy status, and lack of sleep have all been associated with impaired immune function and elevated risk of infection. For example, the likelihood of getting ill is directly linked to the magnitude and duration of stressful events and demeanor.[4] During a 6-month period, for example, the number of sick days is twice as great in high- compared with low-stress groups.[4] Sleep disruption also impairs immune

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Figure 1.

J-Curve Model on the Relationship Between Exercise Workload, and Risk of Upper-Respiratory-Tract Infection (URI).

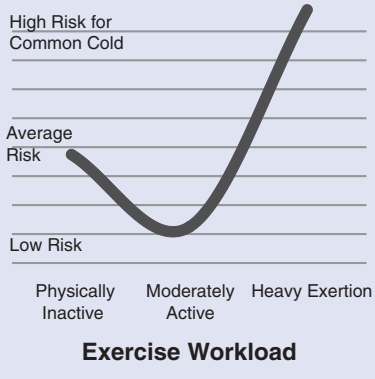
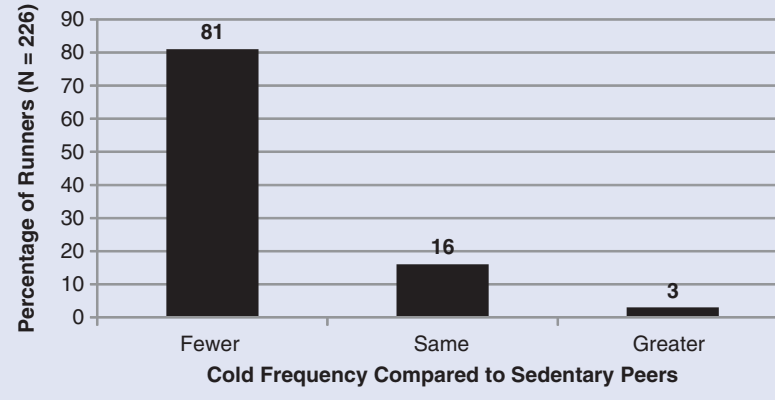


Figure 2.

Survey Responses by WSER athletes in response to this question: "Compared to others who do no run or exercise do you feel that you generally have _____ episodes of sickness with the common cold or flu?" Data From Reference 8. **[AQ: 1]**



function. For example, the antibody response to the flu shot is reduced in individuals experiencing sustained sleep debt.[5] In cold virus challenge studies, thse with a history of poor sleep quality were more prone to illness.[6]

Nutrition has a major influence on your immune function, and nearly all nutrients provide support for the immune system in its work against viruses and bacteria. The best studies, however, indicate that a balanced, healthy diet provides all the nutrients needed for good immune function in most healthy adults, and vitamin/mineral supplements do not boost immunity above normal levels.[7] In general, the concept of boosting immune function through improved lifestyle habits is misleading. A better interpretation of the literature is that a healthy lifestyle supports normal immunity and that poor habits of living impair immune function.

Low- to high-exercise workloads have a unique effect on risk of URI. Regular physical activity improves immune function and lowers URI risk, whereas sustained and intense exertion has the opposite effect. Figure 1 summarizes this J-shaped-curve relationship. This article will emphasize that each moderate exercise bout causes immune system perturbations that enhance immunosurveillance against pathogens and at the same time lowers risk of chronic disease by exerting anti-inflammatory influences.

Moderate Exercise, URI Risk, and Immune Function

Several lines of evidence support the link between moderate physical activity and improved immunity leading to lowered infection rates: survey, animal, epidemiological, and randomized training data. Survey data consistently support the common belief among fitness enthusiasts that regular exercise confers resistance against infection. In surveys, 80% to 90% of regular exercisers perceive themselves as less vulnerable to viral illnesses compared with sedentary peers, as summarized in Figure 2.[8,9]

It is difficult to extrapolate animal studies to the human condition, but in general, they support the finding that moderate exercise lowers morbidity and mortality following pathogen inoculation, especially when compared with prolonged and intense exertion or physical inactivity. Mice infected with the herpes simplex virus, for example, and then exposed to 30 minutes of moderate exercise experience a lower mortality during a 21-day period in contrast to higher mortality rates after 2.5 hours of exhaustive exercise or rest.[10]

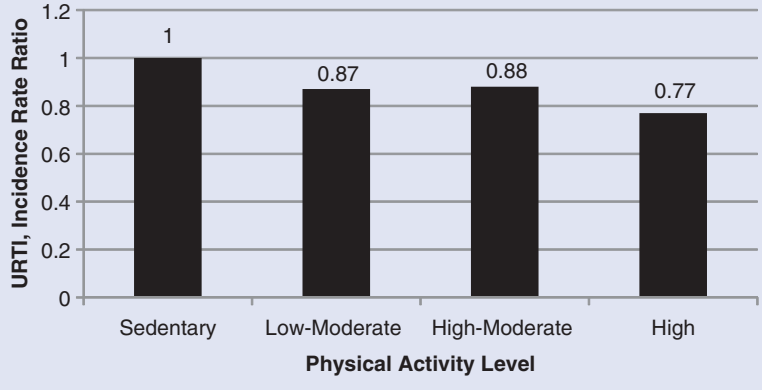
Epidemiological reports have retrospectively or prospectively compared URI incidence in large groups of moderately active and sedentary individuals. Collectively, the epidemiological studies consistently show reduced URI rates in physically active or fit individuals. A 1-year epidemiological study of 547 adults showed a 23% reduction in URI risk in those engaging in regular versus irregular moderate-to-vigorous physical activity, as summarized in Figure 3.[11]

In a group of 145 elderly people, URI symptomatology during a 1-year period was reduced among those engaging in higher compared with lower amounts of moderate physical activity.[12] During a 1-year study of 142 men aged 33 to 90, the odds of having at least 15 days with URI was 64% lower among those with higher physical activity patterns.[13] In Project PRIME, a randomized clinical trial that investigated interventions to increase physical activity, the odds ratio for reporting URI symptoms was 0.50 (95% confidence interval = 0.28 to 0.91) among participants who engaged in a minimum of 150 minutes per week of moderate and vigorous activity compared with less active participants.[14]

A group of 1002 adults (ages 18 to 85 years, 60% female, 40% male) were followed for 12 weeks (half during the

Figure 3.

This 1-Year Study of 547 Adults Showed a 23% Reduction in Upper-Respiratory-Tract Infection (URTI) Risk in Those Engaging in Regular Versus Irregular Physical Activity. Data From Reference 11.



winter, half during the fall) while monitoring URI symptoms and severity using the Wisconsin Upper Respiratory Symptom Survey.[15,16] Participants reported frequency of moderate-to-vigorous aerobic activity and rated their physical fitness level using a 10-point Likert scale. Figure 4 shows that the number of days with URI was significantly reduced by 43% in those reporting an average of 5 or more days of aerobic exercise (20 minute bouts or longer) compared with those who were largely sedentary (≤1 day per week). This relationship occurred after adjustment for important confounders, including age, education level, marital status, gender, BMI, and perceived mental stress. The number of days with URI was reduced by 46% when comparing those in the highest versus lowest tertile for perceived physical fitness, even after adjustment for confounders.

Regular physical activity may lower rates of infection for other types of diseases. For example, women who were regular and active walkers had an 18% lower risk of pneumonia compared with women who walked the least.[17] In the same cohort, women who reported running or jogging more than 2 hours per week had a significantly lower risk of pneumonia compared with women who spent no time running or jogging.[17]

Randomized experimental trials have provided important data in support of the viewpoint that moderate physical activity reduces URI symptomatology. In 1 randomized, controlled study of 36 women (mean age 35 years), those in the exercise group walked briskly for 45 minutes, 5 days a week, and experienced one half the days with URI symptoms during the 15-week period compared with the sedentary control group (5.1 ± 1.2 vs 10.8 ± 2.3 days; $P = .039$).[18]

The effect of exercise training (five 45-minute walking sessions/wk at 60%-75% maximum heart rate) and/or moderate energy restriction (1200-1300 kCal per day) on URI was studied in nonobese, physically active women (N = 30) and obese women (N = 91, body mass index 33.1 ± 0.6 kg/m^2) randomized to 1 of 4 groups: control, exercise, diet, exercise and diet.[19] All participants self-reported symptoms of sickness in health logs, using a precoded checklist. Energy restriction had no significant effect on URI incidence, and those from the 2 exercise groups were contrasted with those from the 2 nonexercise groups. The number of days with symptoms of URI for those in the exercise groups was reduced relative to the nonexercise groups (5.6 ± 0.9 and 9.4 ± 1.1 sickness days, respectively), similar to that of the nonobese, physically active controls (4.8 ± 0.9). Figure 5 summarizes the combined data set from these 2 training studies.[18,19]

A 1-year randomized study of 115 overweight, postmenopausal women showed that those who had regular moderate exercise (166 minutes per week, ~4 days per week) had lowered URI risk compared with controls (who engaged in a stretching program).[20] In the final 3 months of the study, the risk of colds in the control group was more than 3-fold that of the exercise group, as summarized in Figure 6.

During moderate exercise, several positive changes occur in the immune system.[21-24] Moderate exercise increases the recirculation of immunoglobulins, and neutrophils and natural killer cells, 2 cell types that play a critical role in innate immune defenses. Animal data indicate that lung macrophages play an important role in mediating the beneficial effects of moderate exercise on lowered susceptibility to infection.[25] Stress hormones, which can suppress immunity, and pro-inflammatory and anti-inflammatory cytokines, indicative of intense metabolic activity, are not elevated during moderate exercise.

Although the immune system returns to preexercise levels within a few hours after the exercise session is over, each session represents a boost in immune surveillance that reduces the risk of infection over the long term. Other immune-related benefits of exercise include enhanced antibody-specific responses to vaccinations. For example, several studies indicate that both acute and chronic moderate exercise training improve the body's antibody response to the influenza vaccine.[26-29] In 1 study, a 45-minute moderate exercise bout just before influenza vaccination improved the antibody response.[26]

These data provide additional evidence that moderate exercise favorably influences overall immune surveillance against pathogens. Taken together, the data on the relationship between moderate exercise, enhanced immunity, and lowered URI risk are consistent with guidelines urging the general public to engage in near-daily brisk walking.

Exercise-Immune Benefits for Elderly People

Immune senescence or age-associated immune deficiency is partly responsible for some of the afflictions of old age.[30-33]

Figure 4.

The Number of Days With Upper-Respiratory Illness (URI) During a 12-Week Period (Winter or Fall) in a Group of 1002 Adults (Ages 18 to 85 Years) by Various Lifestyle and Demographic Factors. Means Are Adjusted Statistically After Weighting for Each Factor Through a General Linear Model. Data From Reference 15.

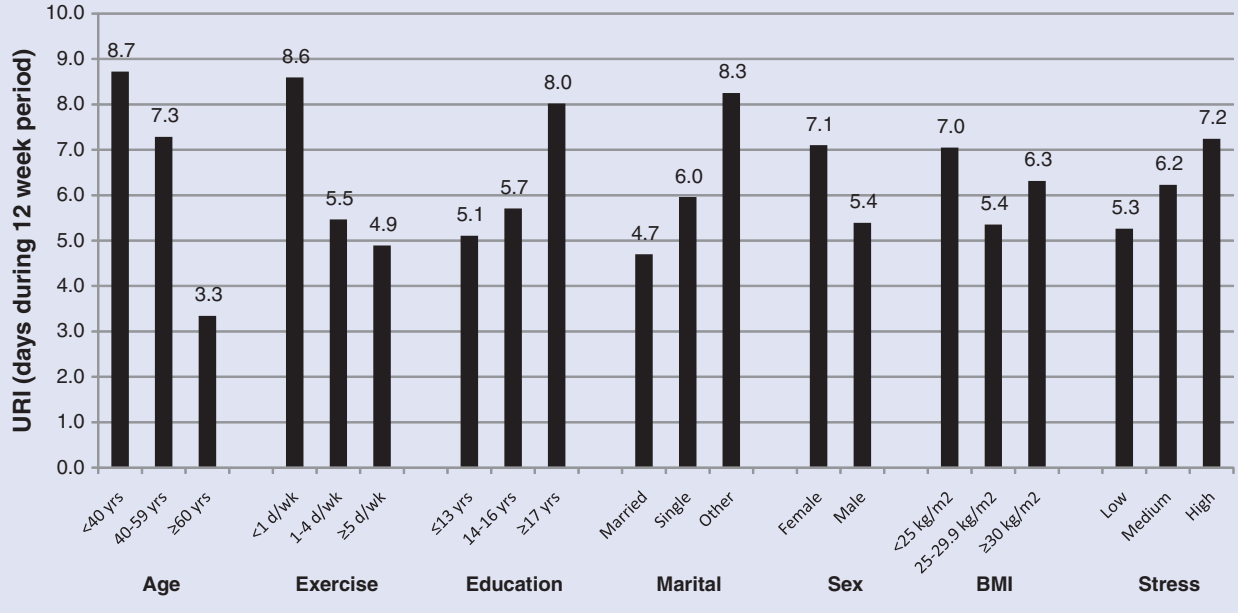


Figure 5.

The Number of Upper-Respiratory Illness (URI) Symptom Days Was Decreased by Approximately Half Through a Walking Program (5 Days Per Week, 45 Minutes Per Session, for 15 Weeks) by Previously Sedentary, Overweight Adult Women. Data Combined From References 18 and 19.

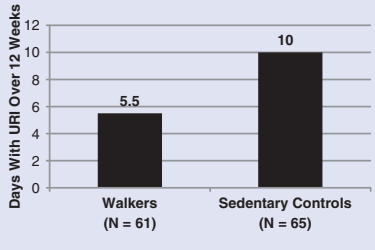
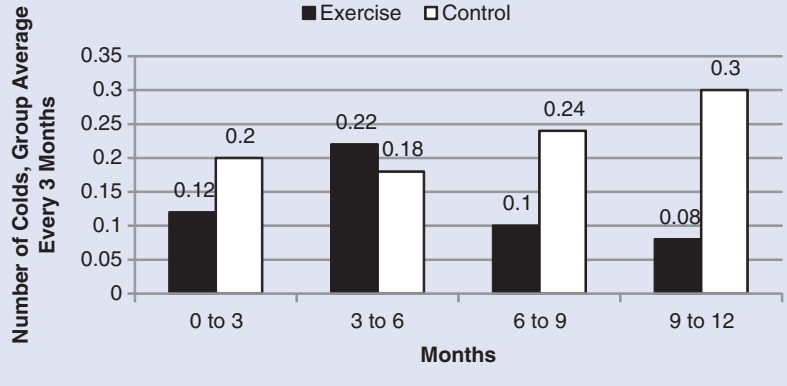


Figure 6.

A 1-Year Randomized Study of 115 Overweight, Postmenopausal Women Showed That 166 Minutes Per Week (~4 d/wk) of Moderate Exercise Lowered Upper-Respiratory Illness Risk Compared With Controls (Stretching), Especially During the Past 3 Months. Data from reference 20.



Elderly persons are more susceptible to vaccine failure and many infections, autoimmune disorders, and cancers when compared with younger adults. The age-related decline is most apparent in T cell–dependent immune functions and is related to thymus involution.[33,34]

Aging is a complex process that ultimately leads to irreversible biological changes. However, health habits can have a sizable influence on life expectancy and quality of life, even in old age.[35] A new and growing area of research is the relationship between certain lifestyle factors (in particular, physical activity and diet) and immune senescence.[35-39]

Older adults exercise less and have lower levels of cardiorespiratory fitness than younger adults, and recent studies indicate that this may contribute to

Figure 7.

T Cell Function (A) and Natural Killer Cell Function (B) in Highly Conditioned Female, Elderly Athletes Compared With Age- and Gender-Matched Sedentary Controls. Data From Reference 44.

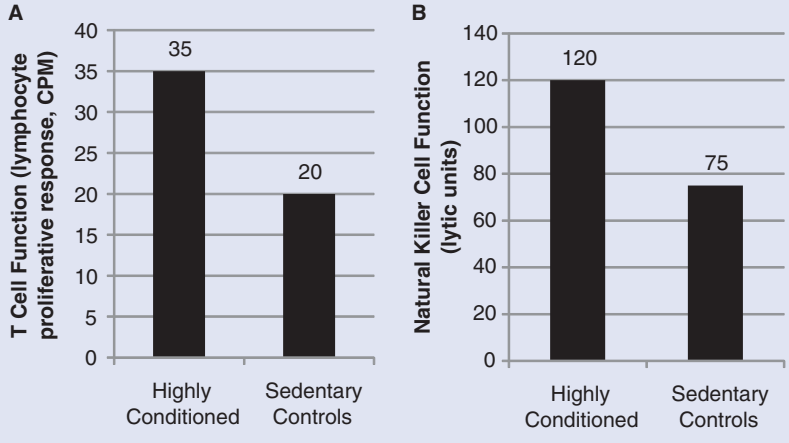
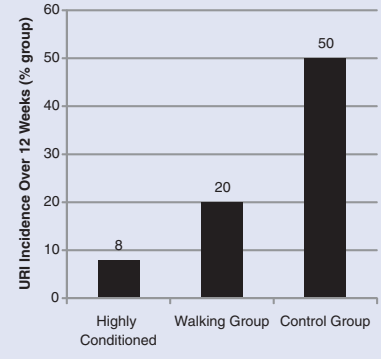


Figure 8.

Upper-Respiratory Illness (URI) Incidence in 3 Groups of Elderly Women During 12 Weeks: Highly Conditioned, Walkers, and Controls. Data From Reference 44.



immune senescence. Acute and chronic physical activity has a major influence on various measures of immune function in older adults according to studies conducted during the past 2 decades.[39-41] Although research on the role of endurance exercise on the immune systems of elderly human subjects is just beginning, data from the few available studies are intriguing and have potential for widespread public health influence.

Several cross-sectional studies have compared immune function in highly conditioned and sedentary elderly (ie, ≥65 years) men and women.[42-44] One study contrasted immune function in 30 sedentary elderly women and 12 age-matched, highly conditioned elderly women (mean age, 73 years) who were active in state and national senior game and road race endurance events.[44] The highly conditioned elderly women (average VO_{2max} of 31 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$) had been physically active for an average of 11 years and had trained an average of 1.6 hours daily during the previous year. The highly conditioned participants exhibited superior function of natural killer and T lymphocytes compared with the 30 sedentary elderly women (Figure 7).

Another study compared immune function in 17 elderly runners, who had trained for about 17 years, and 19 elderly controls, and reported significantly higher T lymphocyte function in the elderly runners.[42] The elderly runners, when compared with the elderly controls, also demonstrated significantly higher rates of interleukin-2 (IL-2), interferon-γ, and IL-4 production from activated T cells. Another cross-sectional study of 13 sedentary and 13 physically active and physically fit older adults (ages 60-76 years) revealed an augmented antibody response to the flu vaccine.[43]

Randomized exercise training studies have investigated the response of the aging immune system to 2 to 6 months of exercise training.[44-50] In 1 study, 30 sedentary elderly women (mean age, 73 years) were assigned to walking or sedentary groups.[44,45] The exercise group walked 30 to 40 minutes, 5 days per week, for 12 weeks at 60% heart rate reserve; 12 weeks of moderate cardiorespiratory exercise improved the VO_{2max} (ie, maximum aerobic fitness) of the previously sedentary elderly participants by 12.6% but did not result in any chronic improvement in natural killer or T cell function relative to the sedentary control group. Incidence of URI in the highly conditioned, walking, and calisthenic control groups was compared during the 12-week study (September through November). Half of the elderly women in the calisthenic group suffered a URI during the study as compared with 3 of 14 women in the walking group and 1 of 12 in the highly conditioned group ($\chi^2 = 6.36$; $P = .042$; Figure 8). Thus, elderly women not engaging in cardiorespiratory exercise were more likely than their exercising counterparts to experience URI during the fall season. Although the initiation of moderate exercise by the elderly did not alter chronic immunity, the acute and transient immune changes during each exercise bout may have improved overall immunosurveillance, decreasing the risk of URI.

A 10-month exercise training study showed that the antibody titer response to the influenza vaccine was increased in elderly adults who had undergone training as compared with sedentary controls[27] (Figure 9). Those who exercised trained at 65% to 75% heart rate reserve, 25 to 30 minutes, 3 days per week. Another 10-month training study with elderly participants showed a significant reduction in inflammatory measures, including IL-6, C-reactive protein (CRP), and IL-18 compared with controls.[46] These data add to the growing consensus that moderate exercise training helps improve vaccine efficacy and counter chronic low-grade inflammation in the elderly.[47]

Collectively, these data from studies of elderly participants provide good support for the role of regular physical activity

as therapy against immune senescence. Physical activity has acute and chronic beneficial effects on the immune systems of elderly people. Cross-sectional studies of highly active, highly conditioned, relatively lean elderly men and women indicate that T cell function is superior to that of their sedentary peers but still below the levels of untrained, young adults. Several 2- to 6-month training studies (both resistance and endurance exercise) have shown that elderly persons can significantly improve strength and aerobic fitness, lower URI rates, and improve vaccine efficacy but without meaningful changes in chronic immune function.[44-49]

These data suggest that each moderate exercise bout by elderly participants causes temporary but positive improvements in immunosurveillance that improve host protection and vaccine antibody responses. Research on the acute effects of moderate exercise suggest that both young and old adults recruit immune cells in a similar fashion, and this increased recirculation of cells may enhance immunosurveillance when physical activity is conducted on a near-daily basis.[50-52]

Exercise Influences on Inflammation and Clinical Outcomes

Acute inflammation is a normal response of the immune system to infection and trauma. Chronic, low-grade inflammation, however, is linked with multiple disorders and diseases, including atherosclerosis and cardiovascular disease (CVD), the metabolic syndrome, diabetes mellitus, sarcopenia, arthritis, osteoporosis, chronic obstructive pulmonary disease, dementia, depression, and various types of cancers.[53-55] CRP is the most frequently measured inflammatory biomarker, and individuals with CRP values in the upper tertile of the adult population (>3.0 mg/L) have a 2-fold increase in CVD risk compared with those with a CRP concentration below 1.0 mg/L.[55]

Large population observational studies show reduced serum CRP and other inflammatory biomarkers (eg, the white blood cell count, IL-6, and tumor necrosis factor [TNF]-α) in adults with higher levels of physical activity and fitness.[56-60] The inverse association between physical activity/fitness with inflammation is related in part to the effect of activity on fat mass.[58] In most studies, however, adjustment for adiposity attenuates but does not negate the strength of the relationship between inflammatory biomarkers and physical activity/fitness.[58]

Figure 9.

Comparison at 1 and 3 Months of Antibody Response to the Influenza Vaccination in Elderly Controls, Elderly Exercisers, and Young Controls. Data From Reference 27.

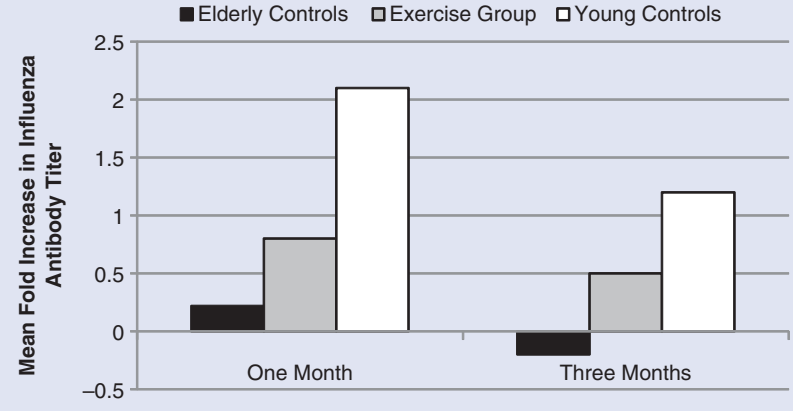
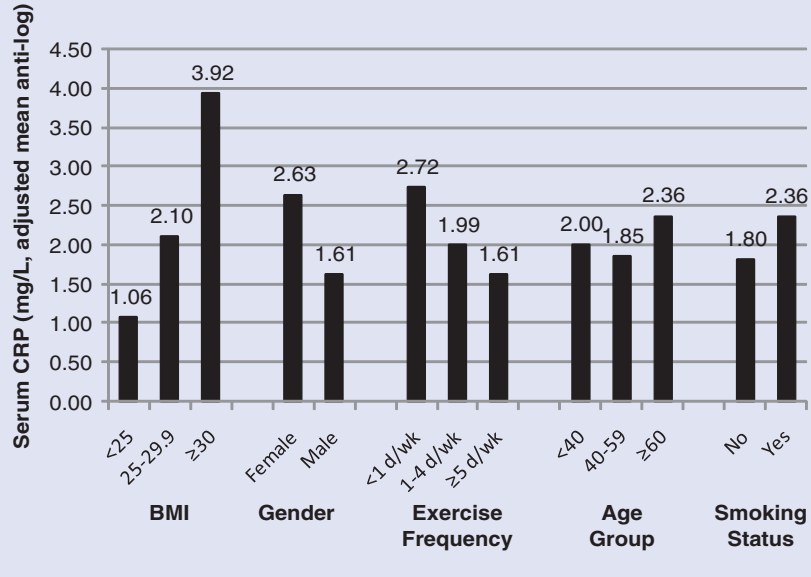


Figure 10.

The Influence of Aerobic Exercise Frequency and Other Lifestyle and Demographic Factors on C-Reactive Protein (CRP). Means Are Adjusted Statistically After Weighting for Each Factor Through a General Linear Model. Data From Reference 61.



In a recent study of 1002 community-dwelling adults (age range, 18- 85 years), a general linear model analysis adjusted CRP means for frequency of physical activity, BMI, and several other lifestyle and demographic factors (Figure 10).[61] As summarized in Figure 10, BMI had the strongest effect on CRP followed by gender,

exercise frequency, age, and smoking status.

An elevated fasting IL-6 concentration is a significant component of the chronic low-grade inflammation that underlies the metabolic syndrome, CVD, diabetes, and various cancers.[62] During prolonged exercise, IL-6 is produced by muscle fibers and stimulates the appearance in the circulation of other anti-inflammatory cytokines such as IL-1ra and IL-10.[63] IL-6 also inhibits the production of the proinflammatory cytokine TNF-α and stimulates lipolysis and fat oxidation.[63] With weight loss from energy restriction and exercise, plasma levels of IL-6 fall, skeletal muscle TNF-α decreases, and insulin sensitivity improves.[64,65] Thus, IL-6 release from the exercising muscle may help mediate some of the health benefits of exercise, including metabolic control of type 2 diabetes.[65] Muscle IL-6 release, however, is very low during moderate physical activity, and additional research is needed to determine if other exercise-induced factors mediate the anti-inflammatory influence of regular physical activity.

Conclusions

By far, the most important finding that has emerged from exercise immunology studies during the past 2 decades is that positive immune changes take place during each bout of moderate physical activity. Over time, this translates to fewer days of sickness with the common cold and other URIs. These data are strengthened by several lines of evidence across both animal and human studies. The 25% to 50% reduction in sick days with near-daily moderate exercise exceeds levels reported for most medications and supplements and bolsters public health guidelines urging individuals to be physically active on a regular basis.

The anti-inflammatory effect of near-daily physical activity may play a key role in many health benefits, including reduced CVD, type 2 diabetes, various types of cancers, sarcopenia, and dementia. This is an exciting area of scientific endeavor, and additional research is needed to determine how immune perturbations during each exercise bout accumulate over time to produce an anti-inflammatory influence. AJLM

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